

Set Name Query
side by sideHit Count Set Name
result set

DB=USPT; PLUR=YES; OP=ADJ

L4 L3 and (flk\$ or tie\$)

2 L4

DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ

L3 L2.clm.

4 L3

L2 (endothelial) same (progenitor\$ or stem\$) same (cd34\$ or flk\$ or tie\$)

208 L2

L1 (endothelial) same (progenitor\$ or stem\$ or cd34\$ or flk\$ or tie\$)

2217 L1

END OF SEARCH HISTORY

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1. Document ID: US 20020051762 A1

L3: Entry 1 of 4

File: PGPB

May 2, 2002

PGPUB-DOCUMENT-NUMBER: 20020051762

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020051762 A1

TITLE: PURIFIED POPULATIONS OF ENDOTHELIAL PROGENITOR CELLS

PUBLICATION-DATE: May 2, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
RAFII, SHAHIN	GREAT NECK	NY	US	
WITTE, LARRY	STORMVILLE	NY	US	
MOORE, MALCOLM A.S.	NEW YORK	NY	US	

US-CL-CURRENT: 424/93.1; 435/325, 435/355, 435/366[Full](#) | [Title](#) | [Citation](#) | [Front](#) | [Review](#) | [Classification](#) | [Date](#) | [Reference](#) | [Sequences](#) | [Attachments](#) | [Claims](#) | [KINIC](#) | [Drawn Desc](#) | [Image](#)

2. Document ID: US 5980887 A

L3: Entry 2 of 4

File: USPT

Nov 9, 1999

US-PAT-NO: 5980887

DOCUMENT-IDENTIFIER: US 5980887 A

TITLE: Methods for enhancing angiogenesis with endothelial progenitor cells

DATE-ISSUED: November 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Isner; Jeffrey M.	Weston	MA		
Asahara; Takayuki	Arlington	MA		

US-CL-CURRENT: 424/93.7; 424/85.1, 424/85.2, 514/44, 514/8[Full](#) | [Title](#) | [Citation](#) | [Front](#) | [Review](#) | [Classification](#) | [Date](#) | [Reference](#) | [Sequences](#) | [Attachments](#) | [Claims](#) | [KINIC](#) | [Drawn Desc](#) | [Image](#)

3. Document ID: US 5744347 A

L3: Entry 3 of 4

File: USPT

Apr 28, 1998

US-PAT-NO: 5744347

DOCUMENT-IDENTIFIER: US 5744347 A

TITLE: Yolk sac stem cells and their uses

DATE-ISSUED: April 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wagner; Thomas E.	Albany	OH		
Antczak; Michael R.	Albany	OH		

US-CL-CURRENT: 435/354; 435/355, 435/378, 435/401, 435/7.21

[Full](#) | [Title](#) | [Citation](#) | [Front](#) | [Review](#) | [Classification](#) | [Date](#) | [Reference](#) | [Sequences](#) | [Attachments](#) | [Claims](#) | [KMC](#) | [Drawn Desc](#) | [Image](#)

 4. Document ID: US 5599703 A

L3: Entry 4 of 4

File: USPT

Feb 4, 1997

US-PAT-NO: 5599703

DOCUMENT-IDENTIFIER: US 5599703 A

TITLE: In vitro amplification/expansion of CD34.sup.+ stem and progenitor cells

DATE-ISSUED: February 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Davis; Thomas A.	Chantilly	VA		
Kessler; Steven	Cupertino	CA		
Robinson; Douglas H.	Washington	DC		

US-CL-CURRENT: 435/373; 424/93.7, 435/385, 435/386

[Full](#) | [Title](#) | [Citation](#) | [Front](#) | [Review](#) | [Classification](#) | [Date](#) | [Reference](#) | [Sequences](#) | [Attachments](#) | [KMC](#) | [Drawn Desc](#) | [Image](#)

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Term	Documents
2.CLM..USPT,PGPB,JPAB,EPAB,DWPI.	4
(L2.CLM.).USPT,PGPB,JPAB,EPAB,DWPI.	4

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WEST**End of Result Set**

L3: Entry 4 of 4

File: USPT

Feb 4, 1997

DOCUMENT-IDENTIFIER: US 5599703 A

TITLE: In vitro amplification/expansion of CD34.sup.+ stem and progenitor cells

CLAIMS:

1. A method of expanding human bone marrow CD34.sup.+ stem and progenitor cells, including primitive stem cells, in vitro comprising the steps of:
 - i) isolating the CD34.sup.+ stem and progenitor cells from human bone marrow;
 - ii) contacting the isolated CD34.sup.+ stem and progenitor cells with porcine microvascular brain endothelial cells; and
 - iii) co-culturing the contacted CD34.sup.+ stem and progenitor cells and endothelial cells in the presence of at least one cytokine in an amount sufficient to support amplification/expansion of said CD34+ stem and progenitor cells.
2. The method according to claim 1, wherein said CD34.sup.+ stem and progenitor cells are contacted with a semi-confluent monolayer of the endothelial cells.
6. A method of engrafting human bone marrow CD34.sup.+ stem and progenitor cells in a human in need of said CD34.sup.+ stem and progenitor cells, said method comprising the steps of:
 - i) isolating CD34.sup.+ stem and progenitor cells from human bone marrow;
 - ii) contacting the isolated CD34.sup.+ stem and progenitor cells with porcine microvascular brain endothelial cells containing a factor or factors that expand the CD34.sup.+ stem and progenitor cells;
 - iii) co-culturing the contacted CD34.sup.+ stem and progenitor cells and endothelial cells in the presence of at least one cytokine in an amount sufficient to support amplification/expansion of said CD34.sup.+ stem and progenitor cells;
 - iv) isolating the amplified/expanded CD34.sup.+ stem and progenitor cells from the culture; and
 - v) infusing the amplified/expanded CD34.sup.+ stem and progenitor cells into said human.
9. A method of amplifying/expanding human CD34.sup.+ bone marrow stem and progenitor cells in vitro which comprises the steps of:
 - i) isolating CD34.sup.+ stem and progenitor cells from human bone marrow;
 - ii) contacting the isolated CD34.sup.+ stem cells and progenitor cells with porcine microvascular brain endothelial cells; and
 - iii) co-culturing the contacted CD34.sup.+ stem cells and progenitor cells and endothelial cells in the presence of a mixture of granulocyte-macrophage colony stimulating factor, interleukin-3, stem cell factor and interleukin-6 in an amount

sufficient to amplify/expand said CD34.sup.+ stem and progenitor cells.

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Term	Documents
FLK\$	0
FLK.USPT.	425
FLKA.USPT.	4
FLKAG.USPT.	1
"FLKAGINTEGER.SUB".USPT.	2
FLKALDLFAPKMVQIDSF.USPT.	1
FLKARTG.USPT.	3
FLKARTGPQ.USPT.	1
FLKARTGQ.USPT.	3
FLKARTGQP.USPT.	3
FLKAS.USPT.	1
(L3 AND (FLK\$ OR TIE\$)).USPT.	2

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 EPO Abstracts Database
 Derwent World Patents Index
 IBM Technical Disclosure Bulletins

Search:

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Search History**DATE: Wednesday, December 04, 2002** [Printable Copy](#) [Create Case](#)

<u>Set Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
side by side		result set	
	<i>DB=USPT; PLUR=YES; OP=ADJ</i>		
<u>L4</u>	L3 and (flk\$ or tie\$)	2	<u>L4</u>
	<i>DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ</i>		
<u>L3</u>	L2.clm.	4	<u>L3</u>
<u>L2</u>	(endothelial) same (progenitor\$ or stem\$) same (cd34\$ or flk\$ or tie\$)	208	<u>L2</u>
<u>L1</u>	(endothelial) same (progenitor\$ or stem\$ or cd34\$ or flk\$ or tie\$)	2217	<u>L1</u>

END OF SEARCH HISTORY

WEST[Generate Collection](#)[Print](#)**Search Results - Record(s) 1 through 2 of 2 returned.**

1. Document ID: US 5980887 A

L4: Entry 1 of 2

File: USPT

Nov 9, 1999

US-PAT-NO: 5980887

DOCUMENT-IDENTIFIER: US 5980887 A

TITLE: Methods for enhancing angiogenesis with endothelial progenitor cells

DATE-ISSUED: November 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Isner; Jeffrey M.	Weston	MA		
Asahara; Takayuki	Arlington	MA		

US-CL-CURRENT: 424/93.7; 424/85.1, 424/85.2, 514/44, 514/8[Full](#) | [Title](#) | [Citation](#) | [Front](#) | [Review](#) | [Classification](#) | [Date](#) | [Reference](#) | [Sequences](#) | [Attachments](#)[KMC](#) | [Draw Desc](#) | [Image](#)

2. Document ID: US 5744347 A

L4: Entry 2 of 2

File: USPT

Apr 28, 1998

US-PAT-NO: 5744347

DOCUMENT-IDENTIFIER: US 5744347 A

TITLE: Yolk sac stem cells and their uses

DATE-ISSUED: April 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wagner; Thomas E.	Albany	OH		
Antczak; Michael R.	Albany	OH		

US-CL-CURRENT: 435/354; 435/355, 435/378, 435/401, 435/7.21[Full](#) | [Title](#) | [Citation](#) | [Front](#) | [Review](#) | [Classification](#) | [Date](#) | [Reference](#) | [Sequences](#) | [Attachments](#)[KMC](#) | [Draw Desc](#) | [Image](#)[Generate Collection](#)[Print](#)

Term	Documents
FLK\$	0
FLK.USPT.	425
FLKA.USPT.	4
FLKAG.USPT.	1
"FLKAGINTEGER.SUB".USPT.	2
FLKALDLFAPKMVQIDSF.USPT.	1
FLKARTG.USPT.	3
FLKARTGPQ.USPT.	1
FLKARTGQ.USPT.	3
FLKARTGQP.USPT.	3
FLKAS.USPT.	1
(L3 AND (FLK\$ OR TIE\$)).USPT.	2

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WEST**End of Result Set**

L4: Entry 2 of 2

File: USPT

Apr 28, 1998

DOCUMENT-IDENTIFIER: US 5744347 A
TITLE: Yolk sac stem cells and their uses

Drawing Description Text (14):

FIG. 8. Murine yolk sac cells express flk-1 by RT-PCR. Lane 1 is YS-EC, and lane 2 is E11.5 as positive control.

Detailed Description Text (82):

Additionally, PCR primers designed from published sequences of murine receptor tyrosine kinases flk-1 and tek were employed in reactions with reverse transcribed RNA. RNA samples included 2 mg total yolk sac cell RNA, 2 mg total COS7 cell RNA, and 100 ng polyA.sup.+ RNA isolated from an 11.5 day mouse embryo. In order to eliminate the possibility that amplified bands represented DNA contamination, yolk sac RNA was subjected to PCR without treatment with reverse transcriptase. Control PCR reactions run with COS7 cell RNA and yolk sac RNA without reverse transcriptase treatment did not show an amplified band. The flk-1 primers used were as follows:

Detailed Description Text (97):

When the murine yolk sac cells were examined for the expression of two additional endothelial markers by RT-PCR, a specific band was detected for flk-1 and tek (FIG. 8 Lane 1 and FIG. 9 Lane 1, respectively). Additionally, when the cells were grown in the presence of hematopoietic growth factors such as SCF and EPO, adult globin message was induced (FIG. 10).

CLAIMS:

17. A method of producing endothelial cells in vitro, comprising culturing, in the presence of a growth factor, a substantially homogeneous population of murine yolk sac stem cells displaying a phenotype of CD34.sup.-, MHC class I.sup.- and MHC class II.sup.- which are capable of forming tubular structures.

35. A method of producing endothelial cells in vitro, comprising culturing, in the presence of a growth factor, a substantially homogeneous population of human yolk sac stem cells displaying a phenotype of CD34.sup.-, MHC class I.sup.- and MHC class II.sup.- which are capable of forming tubular structures.

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Term	Documents
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FLK.USPT.	425
FLKA.USPT.	4
FLKAG.USPT.	1
"FLKAGINTEGER.SUB".USPT.	2
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FLKARTG.USPT.	3
FLKARTGPQ.USPT.	1
FLKARTGQ.USPT.	3
FLKARTGQP.USPT.	3
FLKAS.USPT.	1
(L3 AND (FLK\$ OR TIE\$)).USPT.	2

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L4

Search History**DATE: Wednesday, December 04, 2002** [Printable Copy](#) [Create Case](#)

for multiple files, etc. See HELP ALERT.

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    04dec02 17:28:21 User208760 Session D2229.4
    $0.12    0.022 DialUnits File5
$0.12  Estimated cost File5
    $0.19    0.022 DialUnits File73
$0.19  Estimated cost File73
    $0.07    0.022 DialUnits File155
$0.07  Estimated cost File155
    $0.27    0.022 DialUnits File399
$0.27  Estimated cost File399
    OneSearch, 4 files,  0.087 DialUnits FileOS
$0.65  Estimated cost this search
$0.65  Estimated total session cost   0.087 DialUnits
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File 410:Chronolog(R) 1981-2002/Nov
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? set hi ;set hi
HIGHLIGHT set on as ''
HIGHLIGHT set on as ''
? begin 5,73,155,399
    04dec02 17:28:27 User208760 Session D2229.5
    $0.00    0.074 DialUnits File410
$0.00  Estimated cost File410
$0.01  TELNET
$0.01  Estimated cost this search
$0.66  Estimated total session cost   0.161 DialUnits
```

SYSTEM:OS - DIALOG OneSearch

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File 155:MEDLINE(R) 1966-2002/Nov W3

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File 399:CA SEARCH(R) 1967-2002/UD=13723
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? e au=isner jeffrey
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Ref	Items	Index-term
E1	2	AU=ISNER JEFFEREY M
E2	5	AU=ISNER JEFFERY M
E3	10	*AU=ISNER JEFFREY
E4	313	AU=ISNER JEFFREY M
E5	1	AU=ISNER JEFFREY MICHAEL
E6	1	AU=ISNER JEFFRREY M
E7	1	AU=ISNER JENNIFER

E8 1 AU=ISNER L
E9 3 AU=ISNER M E
E10 2 AU=ISNER M S
E11 1 AU=ISNER M.-E.
E12 1 AU=ISNER M.E.

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? s e1-e6

2 AU=ISNER JEFFERERY M
5 AU=ISNER JEFFERY M
10 AU=ISNER JEFFREY
313 AU=ISNER JEFFREY M
1 AU=ISNER JEFFREY MICHAEL
1 AU=ISNER JEFFRREY M

S1 332 E1-E6

? s s1 and endothelial(10n) (progenitor or stem)

332 S1
305704 ENDOTHELIAL
63350 PROGENITOR
324979 STEM
1330 ENDOTHELIAL(10N) (PROGENITOR OR STEM)

S2 37 S1 AND ENDOTHELIAL(10N) (PROGENITOR OR STEM)

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S3 30 RD S2 (unique items)

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30 S3
5400489 THERAP?
S4 15 S3 AND THERAP?

? rd s4

...completed examining records

S5 15 RD S4 (unique items)

? t s5/7/all

5/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13889304 BIOSIS NO.: 200200518125

Therapeutic angiogenesis for coronary artery disease.

AUTHOR: Freedman Saul Benedict(a); Isner Jeffrey M(a

AUTHOR ADDRESS: (a)Inq.: Mickey Neely, St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA, 02135**USA E-Mail: mneely222@aol.com

JOURNAL: Annals of Internal Medicine 136 (1):p54-71 1 January, 2002

MEDIUM: print

ISSN: 0003-4819

DOCUMENT TYPE: Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: A large body of evidence in animal models of ischemia shows that administration of angiogenic growth factors, either as recombinant protein or by gene transfer, can augment nutrient perfusion through neovascularization. Many cytokines have angiogenic activity; those that have been best studied in animal models and clinical trials are vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Clinical trials of **therapeutic angiogenesis** in patients with end-stage coronary artery disease have shown increases in exercise time and reductions in anginal symptoms and have provided objective evidence of improved perfusion and left ventricular function. Larger-scale placebo-controlled trials have been limited to intracoronary and intravenous administration of recombinant protein and have not yet shown significant improvement in exercise time or angina compared with placebo. Larger-scale placebo-controlled studies of gene transfer are in progress.

Clinical studies are required to determine the optimal dose, formulation, route of administration, and combinations of growth factors and the utility of adjunctive **endothelial progenitor-cell** or **stem-cell** supplementation, to provide safe and effective **therapeutic** myocardial angiogenesis. Determination of which growth factors or cells are required to optimize **therapeutic** neovascularization in an individual patient should be a goal of future research.

5/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13868605 BIOSIS NO.: 200200497426
Constitutive human telomerase reverse transcriptase expression enhances regenerative properties of **endothelial progenitor** cells.
AUTHOR: Murasawa Satoshi; Llevadot Joan; Silver Marcy; **Isner Jeffrey M**; Losordo Douglas W(a); Asahara Takayuki(a)
AUTHOR ADDRESS: (a)St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135**USA E-Mail: douglas.losordo@tufts.edu, asa777@aol.com
JOURNAL: Circulation 106 (9):p1133-1139 August 27, 2002
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: The regulatory molecule for cell life span, telomerase, was modified by human telomerase reverse transcriptase (hTERT) gene transfer to investigate its effect on regenerative properties of **endothelial progenitor** cells (EPCs) in neovascularization. Methods and Results: Telomerase activity was enhanced in hTERT-transduced EPCs (Td-TERTs) (1.2-fold versus no transduced EPCs (no-Td) and 1.2-fold versus GFP-transduced EPCs (Td/GFPs) at day 8; 5.2-fold versus no-Td and 4.8-fold versus Td/GFP at day 21, respectively) Mitogenic capacity in Td/TERTs exceeded that in Td/GFPs at day 8 (0.62+-0.02 versus 0.53+-0.01, respectively; P<0.01). Vascular endothelial growth factor-induced cell migration in EPCs was markedly enhanced by hTERT overexpression (Td/TERTs versus Td/GFPs, 292+-12 versus 174+-6 cells, respectively; P<0.01). hTERT overexpression has rescued EPCs from starvation-induced cell apoptosis, an outcome that was further enhanced in response to vascular endothelial growth factor. The colony appearance of totally differentiated endothelial cells (tdECs) was detected before day 30 only in Td/TERT, whereas no tdEC colonies could be detected in both Td/GFPs and no-Tds. Finally, we investigated *in vivo* transplantation of heterologous EPCs. Td/TERTs dramatically improved postnatal neovascularization in terms of limb salvage by 4-fold in comparison with that of Td/GFPs; limb perfusion was measured by laser Doppler (0.77+-0.10 versus 0.47+-0.06; P=0.02), and capillary density (224+-78 versus 90+-40 capillaries/mm²; P<0.01). Conclusions: These findings provide the novel evidence that telomerase activity contributes to EPC angiogenic properties; mitogenic activity, migratory activity, and cell survival. This enhanced regenerative activity of EPCs by hTERT transfer will provide novel **therapeutical** strategy for postnatal neovascularization in severe ischemic disease patients.

5/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13756849 BIOSIS NO.: 200200385670
Statins **therapy** accelerates reendothelialization: A novel effect

involving mobilization and incorporation of bone marrow-derived endothelial progenitor cells.

AUTHOR: Walter Dirk H; Rittig Kilian; Bahlmann Ferdinand H; Kirchmair Rudolf; Silver Marcy; Murayama Toshinori; Nishimura Hiromi; Losordo Douglas W; Asahara Takayuki(a); Isner Jeffrey M

AUTHOR ADDRESS: (a)St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135**USA E-Mail: asa777@aol.com

JOURNAL: Circulation 105 (25):p3017-3024 June 25, 2002

MEDIUM: print

ISSN: 0009-7322

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Primary and secondary prevention trials suggest that statins possess favorable effects independent of cholesterol reduction. We investigated whether statin **therapy** may also accelerate reendothelialization after carotid balloon injury. Methods and Results: Simvastatin treatment in 34 male Sprague-Dawley rats accelerated reendothelialization of the balloon-injured arterial segments (reendothelialized area at 2 weeks, 12.3+-1.8 versus 5.4+-1.1 mm², P<0.01) and resulted in a dose-dependent (0.2 or 1 mg/kg IP) significant reduction in neointimal thickening at 2, 3, and 4 weeks compared with saline-injected controls (n=18). To elucidate the mechanism, we investigated the contribution of bone marrow-derived **endothelial progenitor** cells (EPCs) by bone marrow transplantation from Tie2/lacZ mice to background mice or nude rats. X-gal staining of mouse carotid artery specimens revealed a 2.9-fold increase in the number of beta-gal-positive cells per square millimeter appearing on the carotid artery luminal surface at 2 weeks, and double-fluorescence immunohistochemistry disclosed a significant 5-fold increase in the number of double-positive cells (beta-gal, isolectin B4) on the luminal surface in carotid arteries of statin-treated nude rats (20+-3 versus 4+-1 cells/mm surface length, P<0.005). Statins increased circulating rat EPCs (2.4-fold at 2 weeks and 2.5-fold at 4 weeks, P<0.001) and induced adhesiveness of cultured human EPCs by upregulation of the integrin subunits alpha5, beta1, alphav, and beta5 of human EPCs as shown by reverse transcription-polymerase chain reaction and fluorescence-activated cell sorting. Conclusions: These findings establish additional mechanisms by which statins may specifically preempt disordered vascular wall pathology and constitute physiological evidence that EPC mobilization represents a functionally relevant consequence of statin **therapy**.

5/7/4 (Item 4 from file: 5)
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13634964 BIOSIS NO.: 200200263785
Statin **therapy** accelerates re-endothelialization by mobilization and incorporation of bone-marrow derived **endothelial progenitor** cells.

AUTHOR: Walter Dirk H(a); Rittig Kilian(a); Bahlmann Ferdinand H(a); Kirchmair Rudolf(a); Silver Marcy(a); Murayama Toshinori(a); Nishimura Hiromi(a); Asahara Takayuki(a); Isner Jeffrey M(a)

AUTHOR ADDRESS: (a)St Elizabeth's Med Ctr, Boston, MA**USA

JOURNAL: Circulation 104 (17 Supplement):pII156 October 23, 2001

MEDIUM: print

CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001

ISSN: 0009-7322

RECORD TYPE: Citation

LANGUAGE: English

5/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13558329 BIOSIS NO.: 200200187150
Endothelial progenitor cell vascular **endothelial growth factor** gene transfer for vascular regeneration.
AUTHOR: Iwaguro Hideki; Yamaguchi Jun-ichi; Kalka Christoph; Murasawa Satoshi; Masuda Haruchika; Hayashi Shin-ichiro; Silver Marcy; Li Tong; Isner Jeffrey M; Asahara Takayuki(a)
AUTHOR ADDRESS: (a)St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135**USA E-Mail: asa777@aol.com
JOURNAL: Circulation 105 (6):p732-738 February 12, 2002
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background-Previous studies have established that bone marrow-derived **endothelial progenitor** cells (EPCs) are present in the systemic circulation. In the current study, we investigated the hypothesis that gene transfer can be used to achieve phenotypic modulation of EPCs. Methods and Results-In vitro, ex vivo murine vascular endothelial growth factor (VEGF) 164 gene transfer augmented EPC proliferative activity and enhanced adhesion and incorporation of EPCs into quiescent as well as activated endothelial cell monolayers. To determine if such phenotypic modulation may facilitate **therapeutic** neovascularization, heterologous EPCs transduced with adenovirus encoding VEGF were administered to athymic nude mice with hindlimb ischemia; neovascularization and blood flow recovery were both improved, and limb necrosis/autoamputation were reduced by 63.7% in comparison with control animals. The dose of EPCs used for the in vivo experiments was 30 times less than that required in previous trials of EPC transplantation to improve ischemic limb salvage. Necropsy analysis of animals that received DII-labeled VEGF-transduced EPCs confirmed that enhanced EPC incorporation demonstrated in vitro contributed to in vivo neovascularization as well. Conclusions-In vitro, VEGF EPC gene transfer enhances EPC proliferation, adhesion, and incorporation into endothelial cell monolayers. In vivo, gene-modified EPCs facilitate the strategy of cell transplantation to augment naturally impaired neovascularization in an animal model of experimentally induced limb ischemia.

5/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13000081 BIOSIS NO.: 200100207230
Vascular endothelial growth factor (VEGF) gene introduction as the promissing strategy in **therapeutic** postnatal neovascularization for ischemic tissue.
AUTHOR: Saito Eiko(a); Iwaguro Hideki(a); Tanaka Etsurou(a); Ando Kiyoshi (a); Nakazawa Hiroe(a); Isner Jeffrey M; Asahara Takayuki; Mori Hidezo(a)
AUTHOR ADDRESS: (a)Depts. of Physiology, Genetic Engineering and Cell Transplantation, Tokai Univ. Sch. of Medicine, Kanagawa, 259-1193**Japan
JOURNAL: Japanese Journal of Pharmacology 85 (Supplement 1):p64P 2001
MEDIUM: print
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RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

5/7/7 (Item 7 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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12955710 BIOSIS NO.: 200100162859
Therapeutic angiogenesis for ischemic cardiovascular disease.
AUTHOR: Freedman Saul Benedict; **Isner Jeffrey M(a)**
AUTHOR ADDRESS: (a)St. Elizabeth's Medical Center, 736 Cambridge St.,
Boston, MA, 02135: VeJeff@aol.com**USA
JOURNAL: Journal of Molecular and Cellular Cardiology 33 (3):p379-393
March, 2001
MEDIUM: print
ISSN: 0022-2828
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In animal models of ischemia, a large body of evidence indicates that administration of angiogenic growth factors, either as recombinant protein or by gene transfer, can augment nutrient perfusion through neovascularization. While many cytokines have angiogenic activity, the best studied both in animal models and clinical trials are vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Clinical trials of **therapeutic angiogenesis** in patients with end-stage coronary artery disease have shown large increases in exercise time and marked reductions in symptoms of angina, as well as objective evidence of improved perfusion and left ventricular function. Larger scale placebo-controlled trials have been limited to intracoronary and intravenous administration of recombinant protein, and have not yet shown significant improvement in either exercise time or angina when compared to placebo. Larger scale placebo-controlled studies of gene transfer are in progress. Future clinical studies will be required to determine the optimal dose, formulation, route of administration and combinations of growth factors, as well as the requirement for **endothelial progenitor** cell or **stem** cell supplementation, to provide effective and safe **therapeutic** myocardial angiogenesis.

5/7/8 (Item 8 from file: 5)
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12917157 BIOSIS NO.: 200100124306
Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia.
AUTHOR: Kawamoto Atsuhiko; Gwon Heon-Cheol; Iwaguro Hideki; Yamaguchi Jun-Ichi; Uchida Shigeki; Masuda Haruchika; Silver Marcy; Ma Hong; Kearney Marianne; **Isner Jeffrey M(a)**; Asahara Takayuki(a)
AUTHOR ADDRESS: (a)St Elizabeth's Medical Center, 736 Cambridge Street,
Boston, MA, 02135: VeJeff@aol.com**USA
JOURNAL: Circulation 103 (5):p634-637 February 6, 2001
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Background: We investigated the therapeutic potential of ex vivo expanded endothelial progenitor cells (EPCs) for myocardial neovascularization. Methods and Results: Peripheral blood mononuclear cells obtained from healthy human adults were cultured in EPC medium and harvested 7 days later. Myocardial ischemia was induced by ligating the left anterior descending coronary artery in male Hsd:RH-rnu (athymic nude) rats. A total of 106 EPCs labeled with 1,1'-dioctadecyl-1 to 3,3,3',3'-tetramethylindocarbocyanine perchlorate were injected intravenously 3 hours after the induction of myocardial ischemia. Seven days later, fluorescence-conjugated Bandeiraea simplicifolia lectin I was administered intravenously, and the rats were immediately killed. Fluorescence microscopy revealed that transplanted EPCs accumulated in the ischemic area and incorporated into foci of myocardial neovascularization. To determine the impact on left ventricular function, 5 rats (EPC group) were injected intravenously with 106 EPCs 3 hours after ischemia; 5 other rats (control group) received culture media. Echocardiography, performed just before and 28 days after ischemia, disclosed ventricular dimensions that were significantly smaller and fractional shortening that was significantly greater in the EPC group than in the control group by day 28. Regional wall motion was better preserved in the EPC group. After euthanization on day 28, necropsy examination disclosed that capillary density was significantly greater in the EPC group than in the control group. Moreover, the extent of left ventricular scarring was significantly less in rats receiving EPCs than in controls. Immunohistochemistry revealed capillaries that were positive for human-specific endothelial cells. Conclusions: Ex vivo expanded EPCs incorporate into foci of myocardial neovascularization and have a favorable impact on the preservation of left ventricular function.

5/7/9 (Item 9 from file: 5)
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12763781 BIOSIS NO.: 200000517404
Angiogenesis and vasculogenesis. Therapeutic approaches for stimulation of post-natal neovascularization.
AUTHOR: Kalka Christoph(a); Asahara Takayuki; Krone Wilhelm; Isner Jeffrey M
AUTHOR ADDRESS: (a)Cardiovascular Research, St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA, 02135**USA
JOURNAL: Herz 25 (6):p611-622 September, 2000
MEDIUM: print
ISSN: 0340-9937
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: English; German

ABSTRACT: The formation of new blood vessel is essential for a variety of physiological processes like embryogenesis and the female reproduction as well as wound healing and neovascularization of ischemic tissue. Major progress in understanding the underlying mechanisms regulating blood vessel growth has offered novel therapeutic options in the treatment of a variety of diseases including ischemic cardiovascular disorders. Vasculogenesis and angiogenesis are the mechanisms responsible for the development of the blood vessels. Angiogenesis refers to the formation of capillaries from preexisting vessels in the embryo and adult organism. While pathologic angiogenesis includes the role of post-natal neovascularization in the pathogenesis of arthritis, diabetic retinopathy, and tumor growth and metastasis, therapeutic angiogenesis, either endogenously or in response to administered growth

factors, includes the development of collateral blood vessels in tissue ischemia. Preclinical studies established that angiogenic growth factors could promote collateral artery development in animal models of peripheral and myocardial ischemia. Subsequent clinical trials using gene transfer of naked DNA encoding for VEGF for the treatment of critical limb and myocardial ischemia documented the safety and clinical benefit of this novel **therapeutic** approach. Several objective methods indicated marked improvement in collateral vessel development. Vasculogenesis describes the development of new blood vessels from in situ differentiating endothelial cells. Recently considered to be restricted to embryogenesis, there exists now striking evidence that **endothelial progenitor** cells (EPC) circulate also in adult peripheral blood able to participate in ongoing neovascularization. Different cytokines and growth factors have a stimulatory effect on these bone-marrow derived EPC. Granulocyte macrophage colony stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF) mobilize EPC from the bone marrow into the peripheral circulation. While their endogenous contribution to postnatal neovascularization needs to be documented, the iatrogenic expansion and mobilization of EPC might represent an effective means to augment the resident population of endothelial cells (ECs). This kind of cell **therapy** for tissue regeneration in ischemic cardiovascular diseases opens a novel and challenging clinical option besides or in addition to the use of growth factors in gene **therapy**

5/7/10 (Item 10 from file: 5)
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12559539 BIOSIS NO.: 200000313041
Vascular **endothelial** growth factor165 gene transfer augments circulating **endothelial progenitor** cells in human subjects.
AUTHOR: Kalka Christoph; Masuda Haruchik; Takahashi Tomono; Gordon Rebecc; Tepper Oren; Gravereaux Edwin; Pieczek Ann; Iwaguro Hideki; Hayashi Shin-Ichiro; Isner Jeffrey M; Asahara Takayuki
AUTHOR ADDRESS: (a)St. Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135**USA
JOURNAL: Circulation Research 86 (12):p1198-1202 June 23, 2000
MEDIUM: print
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Preclinical studies in animal models and early results of clinical trials in patients suggest that intramuscular injection of naked plasmid DNA encoding vascular endothelial growth factor (VEGF) can promote neovascularization of ischemic tissues. Such neovascularization has been attributed exclusively to sprout formation of endothelial cells derived from preexisting vessels. We investigated the hypothesis that VEGF gene transfer may also augment the population of circulating **endothelial progenitor** cells (EPCs). In patients with critical limb ischemia receiving VEGF gene transfer, gene expression was documented by a transient increase in plasma levels of VEGF. A culture assay documented a significant increase in EPCs (219%, P<0.001), whereas patients who received an empty vector had no change in circulating EPCs, as was the case for volunteers who received saline injections (VEGF versus empty vector, P<0.001; VEGF versus saline, P<0.005). Fluorescence-activated cell sorter analysis disclosed an overall increase of up to 30-fold in endothelial lineage markers KDR (VEGF receptor-2), VE-cadherin, CD34, alphavbeta3, and E-selectin after VEGF gene transfer. Constitutive overexpression of VEGF in patients with limb ischemia

augments the population of circulating EPCs. These findings support the notion that neovascularization of human ischemic tissues after angiogenic growth factor **therapy** is not limited to angiogenesis but involves circulating endothelial precursors that may home to ischemic foci and differentiate *in situ* through a process of vasculogenesis.

5/7/11 (Item 11 from file: 5)
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12447047 BIOSIS NO.: 200000200549

Transplantation of ex vivo expanded **endothelial progenitor** cells for **therapeutic** neovascularization.

AUTHOR: Kalka Christoph; Masuda Haruchika; Takahashi Tomono; Kalka-Moll Wiltrud M; Silver Marcy; Kearney Marianne; Li Tong; **Isner Jeffrey M** (a); Asahara Takayuki(a)

AUTHOR ADDRESS: (a)St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA, 02135**USA

JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 97 (7):p3422-3427 March 28, 2000

ISSN: 0027-8424

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Animal studies and preliminary results in humans suggest that lower extremity and myocardial ischemia can be attenuated by treatment with angiogenic cytokines. The resident population of endothelial cells that is competent to respond to an available level of angiogenic growth factors, however, may potentially limit the extent to which cytokine supplementation enhances tissue neovascularization. Accordingly, we transplanted human **endothelial progenitor** cells (hEPCs) to athymic nude mice with hindlimb ischemia. Blood flow recovery and capillary density in the ischemic hindlimb were markedly improved, and the rate of limb loss was significantly reduced. Ex vivo expanded hEPCs may thus have utility as a "supply-side" strategy for **therapeutic** neovascularization.

5/7/12 (Item 12 from file: 5)
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12121188 BIOSIS NO.: 199900416037

Bone marrow origin of **endothelial progenitor** cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization.

AUTHOR: Asahara Takayuki(a); Masuda Haruchika; Takahashi Tomono; Kalka Christoph; Pastore Christopher; Silver Marcy; Kearne Marianne; Magner Meredith; **Isner Jeffrey M**(a)

AUTHOR ADDRESS: (a)St Elizabeth's Medical Center, 736 Cambridge St, Boston, MA, 02135**USA

JOURNAL: Circulation Research 85 (3):p221-228 Aug. 6, 1999

ISSN: 0009-7330

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: Circulating **endothelial progenitor** cells (EPCs) have been isolated in peripheral blood of adult species. To determine the origin and role of EPCs contributing to postnatal vasculogenesis,

transgenic mice constitutively expressing beta-galactosidase under the transcriptional regulation of an endothelial cell-specific promoter (Flk-1/LZ or Tie-2/LZ) were used as transplant donors. Localization of EPCs, indicated by flk-1 or tie-2/lacZ fusion transcripts, were identified in corpus luteal and endometrial neovasculature after inductive ovulation. Mouse syngeneic colon cancer cells (MCA38) were implanted subcutaneously into Flk-1/LZ/BMT (bone marrow transplantation) and Tie-2/LZ/BMT mice; tumor samples harvested at 1 week disclosed abundant flk-1/lacZ and tie-2/lacZ fusion transcripts, and sections stained with X-gal demonstrated that the neovasculature of the developing tumor frequently comprised Flk-1- or Tie-2-expressing EPCs. Cutaneous wounds examined at 4 days and 7 days afterskin removal by punch biopsy disclosed EPCs incorporated into foci of neovascularization at high frequency. One week after the onset of hindlimb ischemia, lacZ-positive EPCs were identified incorporated into capillaries among skeletal myocytes. After permanent ligation of the left anterior descending coronary artery, histological samples from sites of myocardial infarction demonstrated incorporation of EPCs into foci of neovascularization at the border of the infarct. These findings indicate that postnatal neovascularization does not rely exclusively on sprouting from preexisting blood vessels (angiogenesis); instead, EPCs circulate from bone marrow to incorporate into and thus contribute to postnatal physiological and pathological neovascularization, which is consistent with postnatal vasculogenesis.

5/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11981239 BIOSIS NO.: 199900234552
Ischemia- and cytokine-induced mobilization of bone marrow-derived
endothelial progenitor cells for neovascularization.
AUTHOR: Takahashi Tomono; Kalka Christoph; Masuda Haruchika; Chen Donghui;
Silver Marcy; Kearney Marianne; Magner Meredith; **Isner Jeffrey M**(a)
; Asahara Takayuki(a
AUTHOR ADDRESS: (a)Departments of Medicine (Cardiology) and Biomedical
Research, St. Elizabeth's Medical Center, Tu**USA
JOURNAL: Nature Medicine 5 (4):p434-438 April, 1999
ISSN: 1078-8956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Endothelial progenitor** cells (EPCs) have been isolated from circulating mononuclear cells in human peripheral blood and shown to be incorporated into foci of neovascularization, consistent with postnatal vasculogenesis. We determined whether endogenous stimuli (tissue ischemia) and exogenous cytokine **therapy** (granulocyte macrophage-colony stimulating factor, GM-CSF) mobilize EPCs and thereby contribute to neovascularization of ischemic tissues. The development of regional ischemia in both mice and rabbits increased the frequency of circulating EPCs. In mice, the effect of ischemia-induced EPC mobilization was demonstrated by enhanced ocular neovascularization after cornea micropocket surgery in mice with hindlimb ischemia compared with that in non-ischemic control mice. In rabbits with hindlimb ischemia, circulating EPCs were further augmented after pretreatment with GM-CSF, with a corresponding improvement in hindlimb neovascularization. There was direct evidence that EPCs that contributed to enhanced corneal neovascularization were specifically mobilized from the bone marrow in response to ischemia and GM-CSF in mice transplanted with bone marrow from transgenic donors expressing beta-galactosidase transcriptionally regulated by the endothelial cell-specific Tie-2 promoter. These findings

indicate that circulating EPCs are mobilized endogenously in response to tissue ischemia or exogenously by cytokine **therapy** and thereby augment neovascularization of ischemic tissues.

5/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10830378 BIOSIS NO.: 199799451523
Isolation of putative **progenitor endothelial** cells for angiogenesis.
AUTHOR: Asahara Takayuki; Murohara Toyoaki; Sullivan Alison; Silver Marcy;
Van Der Zee Rien; Li Tong; Witzenbichler Bernhard; Schatteman Gina;
Isner Jeffrey M
AUTHOR ADDRESS: (a)Dep. Biomed. Res., St. Elizabeth's Med. Center, Tufts
Univ. Sch. Med., 736 Cambridge St., Boston**USA
JOURNAL: Science (Washington D C) 275 (5302):p964-967 1997
ISSN: 0036-8075
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Putative endothelial cell (EC) progenitors or angioblasts were isolated from human peripheral blood by magnetic bead selection on the basis of cell surface antigen expression. In vitro, these cells differentiated into ECs. In animal models of ischemia, heterologous, homologous, and autologous EC progenitors incorporated into sites of active angiogenesis. These findings suggest that EC progenitors may be useful for augmenting collateral vessel growth to ischemic tissues (**therapeutic** angiogenesis) and for delivering anti- or pro-angiogenic agents, respectively, to sites of pathologic or utilitarian angiogenesis.

5/7/15 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13111503 21979722 PMID: 11983091
Endothelial progenitor cells for vascular regeneration.
Asahara Takayuki; **Isner Jeffrey M**
Cardiovascular Research and Medicine, St. Elizabeth's Medical Center,
Tufts University School of Medicine, Boston, MA 02135.
Journal of hematology & stem cell research (United States) Apr 2002,
11 (2) p171-8, ISSN 1525-8165 Journal Code: 100892915
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The basis for native as well as **therapeutic** neovascularization is not restricted to angiogenesis but includes postnatal vasculogenesis. Our laboratory and others' have established that bone marrow-derived **endothelial progenitor** cells (EPCs) are present in the systemic circulation, are augmented in response to certain cytokines and/or tissue ischemia, and home to as well as incorporate into sites of neovascularization. Given the background, EPCs have been investigated as **therapeutic** agents in these studies of supply-side angiogenesis under pathological as well as physiological conditions. This review discusses the **therapeutic** potential of EPCs for cardiovascular ischemic diseases.

Record Date Created: 20020501

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9/7/33 (Item 16 from file: 155)
DIALOG(R) File 155: MEDLINE(R)

13278186 21995347 PMID: 11998334

Angiogenesis therapy in ischemic disease.

Silvestre J S; Levy B I

INSERM U541, hopital Lariboisiere, institut federatif de recherche circulation-Paris 7, universite Paris 7-Denis Diderot, 75475 Paris.

Archives des maladies du coeur et des vaisseaux (France) Mar 2002

, 95 (3) p189-96, ISSN 0003-9683 Journal Code: 0406011

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The ability of organisms to spontaneously develop collateral vessels represents an important response to vascular occlusive diseases that determines the severity of residual tissue ischemia. Neovascularization of ischemic cardiac or skeletal muscle may be sufficient to preserve tissue integrity and/or function, and may thus be considered to be therapeutic. Innovative gene technologies and advances in animal modeling have enabled research scientists to develop therapeutic angiogenesis strategies applied in animal models of limb or myocardial ischemia and in treatment of patients with peripheral vascular obstruction or coronary artery diseases. Several therapeutic strategies have been proposed and tested even at the clinical level. Recent studies have established the feasibility of using recombinant angiogenic growth factors (mainly VEGF and FGF) to enhance angiogenesis in patients with limb or myocardial ischemia. Angiogenesis therapies using cells as a support for growth factor delivery or using endothelial progenitor cells which may directly participate in the angiogenic process have also been developed. Finally, one potential alternative strategy may be the use of drugs with pro-angiogenic activity, available in an oral formulation and which are currently administered to patients for treatment of different pathologies. All strategies of angiogenesis therapy currently being tested have the potential to be effective in the treatment of ischemic disease. However, such strategies may cause harmful side effects which emphasize the need to be aware of the biological effects of each angiogenic agent proposed for clinical studies.

(53 Refs.)

Record Date Created: 20020509

Set	Items	Description
S1	332	E1-E6
S2	37	S1 AND ENDOTHELIAL(10N) (PROGENITOR OR STEM)
S3	30	RD S2 (unique items)
S4	15	S3 AND THERAP?
S5	15	RD S4 (unique items)
S6	2810	ENDOTHELIAL AND GENE(W) THERAPY
S7	647	ENDOTHELIAL (10N) GENE(W) THERAPY
S8	94	ENDOTHELIAL (10N) GENE(W) THERAPY AND PY=2002
S9	71	RD S8 (unique items)
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Set	Items	Description
S1	289	E1-E6
S2	156	S1 AND ENDOTHELIAL
S3	150	RD S2 (unique items)
S4	35	S3 AND MITOGEN?
S5	35	RD S4 (unique items)
S6	0	S5 AND PROGENITOR?
S7	1	S5 AND NUCLEIC(W)ACID?
S8	405	(ENDOTHELIAL) (5N) (PROGENITOR? OR CELL? OR STEM?) AND (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR)
S9	389	RD (unique items)
S10	25	S9 AND PY=1994
S11	57	S9 AND PY=1995
S12	57	RD S11 (unique items)
S13	0	(ENDOTHELIAL) (5N) (PROGENITOR? OR STEM?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR) (20N) (TOGETHER OR COMPOSITION)
S14	1	(ENDOTHELIAL) (5N) (PROGENITOR? OR STEM?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR)
S15	206	(ENDOTHELIAL) (5N) (CELL?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR)
S16	3	(ENDOTHELIAL) (5N) (CELL?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR) (20N) (COMPOSITION? OR FORMULATION? OR TOGETHER OR COMBIN?)
S17	2	RD S16 (unique items)

DA/228020

09775281 BIOSIS NO.: 199598230199

Porcine brain microvascular endothelial cells support the in vitro expansion of human primitive hematopoietic bone marrow progenitor cells with a high replating potential: Requirement for cell-to-cell interactions and colony-stimulating factors.

AUTHOR: Davis Thomas A(a); Robinson Dougls H; Lee Kelvin P; Kessler Steven W

AUTHOR ADDRESS: (a) Immune Cell Biol. Program, Naval Med. Res. Inst., 8901 Wisconsin Ave., Bethesda, MD 20889-5055**USA

JOURNAL: Blood 85 (7):p1751-1761 1995

ISSN: .0006-4971

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Primary autologous as well as allogeneic and xenogeneic stroma will support human **stem cell** proliferation and differentiation for several months. In the present study, we investigated the capacity of porcine microvascular **endothelial cells** (PMVECs) **together** with **combinations** of cytokines (granulocyte-macrophage colony-stimulating **factor** (GM-CSF) + **stem cell factor** (SCF), interleukin-3 (IL-3) + SCF + IL-6, and GM-CSF + IL-3 + SCF + IL-6) to support the expansion and development of purified human CD34+ bone marrow cells. In short-term cultures (7 days), the greatest expansion of nonadherent hematopoietic cells and clonogenic progenitors was seen with CD34+ cells in direct contact with PMVEC monolayers (PMVEC contact), followed by PMVEC noncontact and liquid suspension cultures, respectively. Maximal expansion of nonadherent cells (42-fold) and total CD34+ cells (12.6-fold) occurred in PMVEC contact cultures treated with GM-CSF + IL-3 + SCF + IL-6, with similar increases in the number of granulocyte-macrophage colony-forming units (CFU-GM), CFU-mix, erythroid burst-forming units (BFU-E), CFU-blast and CFU-megakaryocyte (CFU-Mk) progenitor cells. Moreover, the number of CD34+ CD38- and CD34+ CD38+ cells increased 148.1-fold and 8.0-fold, respectively. Replating studies show that cells from day 7 dispersed blast cell colonies generated on cytokine-treated PMVEC monolayers have a high replating potential for multilineage progenitor cells. In long-term PMVEC contact cultures, CD34+ cells seeded onto PMVEC monolayers with GM-CSF + IL-3 + SCF + IL-6 showed a total calculated expansion of over 5,000,000-fold of nonadherent cells over 35 days in culture. Maximal clonogenic cell production was observed at day 28, with 6,353-fold for total CFC and comparable increases for CFU-GM, CFU-mix, CFU-blast, BFU-E, and CFU-Mk. The total number of CD34+ cells increased 2,584-fold at day 28. Furthermore, the extended growth kinetics of these cultures indicates that these phenotypically primitive progenitor cells are also functionally expanded on PMVEC monolayers. These results support the hypothesis that direct contact with a PMVEC monolayer supports the initial expansion of hematopoietic progenitor cells with a high replating potential and, possibly, a more primitive phenotype (CD34+, CD34+/CD38-).

23/7/7 (Item 7 from file: 5)
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09948528 BIOSIS NO.: 199598403446
Detection of ELISA of laminin released by endothelial cells from a collagen coated layer of matrigel.
AUTHOR: Ross Lisa L; Laurens Antonio(a)
AUTHOR ADDRESS: (a)Glaxo Inc., Res. Inst., Room 5-4207, 5 Moore Dr., Research Triangle Park, NC 27709**USA
JOURNAL: Methods in Cell Science 17 (1):p47-52 1995
ISSN: 1381-5741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have developed an in vitro model system quantitating the degradation of extracellular matrix by endothelial cells. Collagen is layered over a reconstituted basement membrane matrix (Matrigel) and the release of laminin contained in the Matrigel into the media by endothelial cells is quantitated by ELISA. The cell-specific release of laminin is consistent and reproducible. Incubating an equivalent number of dead endothelial cells in the same manner results in no release of laminin relative to media controls. The cell-specific laminin release is abolished by removing the exogenous growth factor component of the media and plating the cells in media plus 10% serum. Cells plated onto wells coated with collagen alone do not release laminin into the media, indicating that no de novo synthesis and release of laminin occurs during the time frame of the experiment, and that some **factor** or **combination** of factors present in the media supplement is essential for the **endothelial cells** to release laminin degrading

23/7/5 (Item 5 from file: 5)
DIALOG(R) File 5:Biosis Previews(R)
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09961065 BIOSIS NO.: 199598415983
Isolation and cultivation of porcine brain capillary endothelial cells as
an in vitro model of the blood-brain barrier.
AUTHOR: Bobilya D J(a); D'Amour K; Palmer A; Skeffington C; Therrien N;
Tibaduiza E C
AUTHOR ADDRESS: (a)Dep. Animal Nutritional Sci., College Life Sciences
Agric., Kendall hall, University New Hampshi**USA
JOURNAL: Methods in Cell Science 17 (1):p25-32 1995
ISSN: 1381-5741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Capillary endothelial cells were isolated from the brains of Yucatan miniature swine and were cultivated to serve as an in vitro model for blood-brain barrier studies. The procedure included mechanical and enzymatic digestion of the brain tissue followed by separation of the capillary **cells**, based on size and density, from contaminating **cell** types. The purity of the cultures was further enhanced by manipulating the growth medium **composition**. The **cells** possess typical capillary **endothelial cell** morphology, the **Factor VIII** related antigen, and the ability to accumulate acetylated low-density lipoprotein. **Cells** from passages 4-6 were grown on polycarbonate membranes suspended between two chambers of media: analogous to the capillary lumen and the interstitium of the brain. A barrier was established within 4 days, as demonstrated by a resistance to the passage of albumin and an electrical current.

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10071070 BIOSIS NO.: 199598525988

Changes associated with tyrosine phosphorylation during short-term hypoxia
in retinal microvascular endothelial cells in vitro.

AUTHOR: Koroma Barba M; De Juan Eugene Jr

AUTHOR ADDRESS: Wilmer Eye Inst., Johns Hopkins Univ. Sch. Med., Maumenee
721, 600 N. Wolfe St., Baltimore, MD 21287**USA

JOURNAL: Journal of Cellular Biochemistry 59 (1):p123-132 1995

ISSN: 0730-2312

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The occlusion of capillary vessels results in low oxygen tension
in adjacent tissues which triggers a signaling cascade that culminates in
neovascularization. Using bovine retinal capillary endothelial cells
(BRCEC), we investigated the effects of short-term hypoxia on DNA
synthesis, phosphotyrosine induction, changes in the expression of basic
fibroblast growth factor receptor (bFGFR), protein kinase C (PKC-alpha),
heat shock protein 70 (HSP70), and SH2-containing protein (SHC). The
effect of protein tyrosine kinase (PTK) and phosphatase inhibitors on
hypoxia-induced phosphotyrosine was also studied. Capillary endothelial
cells cultured in standard normoxic ($pO_2 = 20\%$) conditions were quiesced
in low serum containing medium and then exposed to low oxygen tension or
hypoxia ($O_2 = 3\%$) in humidified, 5% CO₂, 37 degree C, tissue culture
chambers, on a time-course of up to 24 h. DNA synthesis was potentiated
by hypoxia in a time-dependent manner. This response positively
correlated with the cumulative induction of phosphotyrosine and the
downregulation of bFGFR (M-r apprx 85 kDa). Protein tyrosine kinase
inhibitors, herbimycin-A, and methyl 2,5-dihydroxycinnamate, unlike
genistein, markedly blocked hypoxia-induced phosphotyrosine. Prolonged
exposure of **cells** to phosphatase inhibitor, sodium orthovanadate,
also blocked hypoxia-induced phosphotyrosine. The expression of HSP70,
PKC-alpha, and SHC were not markedly altered by hypoxia. Taken
together, these data suggest that short-term hypoxia activates
endothelial cell proliferation in part via tyrosine
phosphorylation of **cellular** proteins and changes in the expression
of the **FGF** receptor. Thus, **endothelial cell** mitogenesis
and neovascularization associated with low oxygen tension may be
controlled by abrogating signaling pathways mediated by protein tyrosine
kinase and phosphatases.

27/7/1 (Item 1 from file: 5)
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09625747 BIOSIS NO.: 199598080665
Selective platelet-derived growth factor receptor kinase blockers reverse sis-transformation.
AUTHOR: Kovalenko Marina; Gazit Aviv; Boehmer Annette; Rorsman Charlotte;
Ronnstrand Lars; Heldin Carl-Henrik; Waltenberger Johannes; Boehmer
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AUTHOR ADDRESS: Max-Planck Soc., Res. Group "Growth Factor Signal
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ABSTRACT: A novel class of tyrosine kinase blockers represented by the tyrphostins AG1295 and AG126 is described. These compounds inhibit selectively the platelet-derived growth **factor** (PDGF) receptor kinase and the PDGF-dependent **DNA** synthesis in Swiss 3T3 cells and in porcine aorta **endothelial** cells with 50% inhibitory concentrations below 5 and 1 mu-M, respectively. The PDGF receptor blockers have no effect on epidermal growth **factor** receptor autophosphorylation; weak effects on **DNA** synthesis stimulated by insulin, by epidermal growth **factor**, or by a **combination** of both; and over an order of magnitude weaker blocking effect on fibroblast growth **factor**-dependent **DNA** synthesis. AG1296 potently inhibits signaling of human PDGF alpha- and beta-receptors as well as of the related **stem** cell **factor** receptor (c-Kit) but has no effect on autophosphorylation of the vascular **endothelial** growth **factor** receptor KDR or on **DNA** synthesis induced by vascular **endothelial** growth **factor** in porcine aortic **endothelial** cells. Treatment by AG1296 reverses the transformed phenotype of sis-transfected NIH 3T3 cells but has no effect on src-transformed NIH 3T3 cells or on the activity of the kinase p60-c-src(FS27) immunoprecipitated from these **cells**. These potent and selective compounds represent leads for the development of novel agents to combat tumors driven by PDGF or to inhibit PDGF action in other diseases in

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Growth factors and corneal endothelial cells: I. Stimulation of bovine corneal endothelial cell DNA synthesis by defined growth factors

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Peptide growth factors and other physiological growth modifiers were evaluated for their ability to stimulate DNA synthesis in early passage cultures of bovine corneal endothelial cells (BCEC). Increasing concentrations of newborn bovine serum (0.5-10%) causes a progressive increase in DNA synthesis, which approached a plateau at 10% serum. Supplementing medium with 10% serum from different lots of newborn bovine serum or fetal bovine serum stimulated significantly different levels of DNA synthesis by BCEC. Addition of epidermal growth factor (EGF) (2 nM) to medium containing 10% newborn or fetal bovine serum further increased DNA synthesis. Dose-response curves for EGF, transforming growth factor-alpha, basic fibroblast growth factor (bFGF), and insulin-like growth factor I showed that each significantly stimulated high levels of DNA synthesis (200-700% increase) compared with BCEC cultured in serum-free medium. Vaccinia growth factor, insulin, and transforming growth factor-beta each significantly stimulated lower levels of DNA synthesis (30-200% increase), whereas nerve growth factor, multiplication stimulating activity, and platelet-derived growth factor all failed to significantly stimulate DNA synthesis above the level of serum-free medium. Other physiological growth modifiers were tested for their effects on DNA synthesis of BCEC. Transferrin and low levels of 3',5'-cyclic monophosphate (cAMP) stimulated very low levels of DNA synthesis (50% increase) whereas linoleic acid, high levels of selenium, or cAMP each inhibited DNA synthesis 25-75% below the level of BCEC cultured in serum-free medium. A series of eight formulations containing various combinations of EGF, FGF, insulin, transferrin, selenium, linoleic acid, retinoic acid, cAMP, heparin, and endothelial cell growth factor were tested for their mitogenic action on BCEC cultures. A formulation containing EGF, insulin, transferrin, selenium, and linoleic acid (EGF + ITSL) stimulated the highest level of DNA synthesis of BCEC, which was ~25% higher than the increase stimulated by addition of 10% newborn bovine serum. The formulation consisting of EGF + ITSL was also evaluated as a supplement to corneal storage media. Addition of EGF + ITSL to three corneal storage media (McC Carey-Kaufman, K-Sol, CSM) significantly stimulated increases in cell numbers of ~50% above the unsupplemented corneal storage media. These results demonstrate that BCEC respond selectively to different defined peptide growth factors and physiological growth modifiers, and suggest that supplementation of corneal storage media with a defined formulation (EGF + ITSL) may enhance corneal endothelial cell density.

Extracellular ATP and ADP stimulate proliferation of porcine aortic smooth muscle cells

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The mitogenic effect of extracellular ATP on porcine aortic smooth muscle cells (SMC) was examined. Stimulation of (^{sup} 3H)thymidine incorporation by ATP was dose-dependent; the maximal effect was obtained at 100 μM. ATP acted synergistically with insulin, IGF-1, EGF, PDGF, and various other mitogens. Incorporation of (^{sup} 3H)thymidine was correlated with the fraction of (^{sup} 3H)thymidine-labeled nuclei and changes in cell counts. The stimulation of proliferation was also determined by measurement of cellular DNA using bisbenzamide and by following the increase of mitochondrial dehydrogenase protein. The effect of ATP was not due to hydrolysis to adenosine, which shows synergism with ATP. ATP acted as a competence factor. The mitogenic effect of ATP, but not adenosine, was further increased by lysophosphatidate, phosphatidic acid, or norepinephrine. The inhibitor of adenosine deaminase, EHNA, stimulated the effect of adenosine but not ATP. The adenosine receptor antagonist theophylline depressed adenosine-induced mitogenesis. ADP and the non-hydrolyzable analogue adenosine 5'-(beta, gamma-imido)triphosphate (AMP-PNP) were equally mitogenic. Thus extracellular ATP stimulated mitogenesis of SMC via P(2Y) purinoceptors. The mechanism of ATP acting as a mitogen in SMC was further explored. Extracellular ATP stimulated the release of (^{sup} 3H)arachidonic acid (AA) and prostaglandin Einf 2 (PGEinf 2) into the medium, and enhanced cAMP accumulation in a dose-dependent fashion similar to ATP-induced (^{sup} 3H)thymidine incorporation. Inhibitors of the arachidonic acid metabolism pathway, quinacrine and indomethacin, partially inhibited the mitogenic effect of ATP but not of adenosine. Pertussis toxin inhibited ATP-stimulated DNA synthesis, AA release, PGEinf 2 formation, and cAMP accumulation. Down-regulation of protein kinase C (PKC) by long-term exposure to phorbol dibutyrate (PDBu) partially prevented stimulation of DNA synthesis and activation of the AA pathway by ATP. The PKC inhibitor, staurosporine, antagonized mitogenesis stimulated by ATP. No synergistic effect was found when PDBu and ATP were added together. Therefore, a dual mechanism, including both arachidonic acid metabolism and PKC, is involved in ATP-mediated mitogenesis in SMC. In addition, ATP acted synergistically with angiotensin II, phospholipase C, serotonin, or carbachol to stimulate DNA synthesis. Finally, the possible physiological significance of ATP as a **mitogen** in SMC was further studied. The effect of endothelin and heparin, which are released from **endothelial cells**, on ATP-dependent mitogenesis was investigated. Extracellular ATP acted synergistically with endothelin to stimulate a greater extent of (^{sup} 3H)thymidine incorporation than was seen with PDGF plus endothelin. Heparin, believed to have a regulatory role, partially inhibited the stimulation of DNA synthesis caused both by ATP and PDGF. Evidence in the literature indicates that SMC and endothelial cells secrete ATP, ADP, IGF-1, endothelin, and PDGF. These data all suggest a role for ATP and ADP in regulation of SMC, vascular wound repair,

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Effects of growth factors on wound healing in serum-deprived kitten corneal endothelial cell cultures
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The influence of epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF) I and II on wound healing was investigated in a corneal endothelial system with minimal mitotic activity, using serum-deprived kitten corneal endothelial-cell cultures. After wounding, growth factors were added and wound diameter was evaluated. The DNA synthesis was determined by sup 3H-thymidine labeling. Wounds did not close in the control cultures grown in serum-free medium without growth factors. The IGF I or II, alone (10 and 100 ng/ml) or added (10 ng/ml) to EGF or bFGF, had no significant effect on wound closure or thymidine uptake. With EGF or bFGF (10 ng/ml), wounds closed after 15 days. Wounds closed after 10 days with EGF or bFGF (100 ng/ml) alone or with the combination of EGF and bFGF (each at 10 ng/ml). **Combined** EGF and bFGF (each at 100 ng/ml) did not enhance wound closure further. Thymidine uptake was significantly higher in cultures treated with EGF or bFGF (10 ng/ml) than in controls. The uptake could be increased, if both growth factors were **combined**, but only to the same level achieved with a single **factor** at 100 ng/ml. This study showed that EGF and bFGF, but not IGF I or II, enhanced wound closure and DNA synthesis in a corneal **endothelial cell** system that had minimal mitotic activity.

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Growth factors induced vascular endothelial cell proliferation in vitro
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Chinese Ophthalmic Research (CHIN. OPHTHALMIC RES.) (China) 2001,
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NUMBER OF REFERENCES: 14

Objective: To demonstrate the effects of growth factors on the vascular **endothelial** proliferation. The possible roles and synergistic effect of growth factors on retinal neovascular disorders. Methods: Vascular **endothelial** growth **factor** (VEGF) and basic fibroblastic growth **factor** (bFGF) were used to induce the proliferation of vascular endothelium in vitro. The regulatory effects of VEGF and bFGF on endothelium DNA synthesis, **cell** growth and **cell** phases were studied. The synergistic effect of two factors was also investigated. Results Both VEGF and bFGF significantly induced the **endothelial** proliferation in vitro in a dose dependent manner. In **combination**, a synergistic effect was produced. Both factors significantly increased the CPM of SUP3H-TdR in endothelial **cells**. A synergistic effect was also observed in **combination** of two factors. Both growth factors induced increase of **cell** population in S phase. Conclusion: VEGF and bFGF can induce vascular endothelial proliferation and promote DNA synthesis. It is suggested that both factors may possibly be involved in the etiology of

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Therapeutic angiogenesis for ischemic cardiovascular disease
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In animal models of ischemia, a large body of evidence indicates that administration of angiogenic growth factors, either as recombinant protein or by gene transfer, can augment nutrient perfusion through neovascularization. While many cytokines have angiogenic activity, the best studied both in animal models and clinical trials are vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Clinical trials of **therapeutic** angiogenesis in patients with end-stage coronary artery disease have shown large increases in exercise time and marked reductions in symptoms of angina, as well as objective evidence of improved perfusion and left ventricular function. Larger scale placebo-controlled trials have been limited to intracoronary and intravenous administration of recombinant protein, and have not yet shown significant improvement in either exercise time or angina when compared to placebo. Larger scale placebo-controlled studies of gene transfer are in progress. Future clinical studies will be required to determine the optimal dose, formulation, route of administration and combinations of growth factors, as well as the requirement for **endothelial progenitor** cell or **stem** cell supplementation, to provide effective and safe **therapeutic** myocardial angiogenesis. (c) 2001 Academic Press.

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DIALOG(R) File 5:Biosis Previews(R)
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Stem cell **therapy** and gene transfer for regeneration.
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SUMMARY LANGUAGE: English

ABSTRACT: The committed stem and progenitor cells have been recently isolated from various adult tissues, including hematopoietic stem cell, neural **stem** cell, mesenchymal **stem** cell and **endothelial progenitor** cell. These adult **stem** cells have several advantages as compared with embryonic stem cells as their practical **therapeutic** application for tissue regeneration. In this **review**, we discuss the promising gene **therapy** application of adult stem and progenitor cells in terms of modifying stem cell potency, altering organ property, accelerating regeneration and forming expressional organization.

Set	Items	Description
S1	289	E1-E6
S2	156	S1 AND ENDOTHELIAL
S3	150	RD S2 (unique items)
S4	35	S3 AND MITOGEN?
S5	35	RD S4 (unique items)
S6	0	S5 AND PROGENITOR?
S7	1	S5 AND NUCLEIC(W)ACID?
S8	405	(ENDOTHELIAL) (5N) (PROGENITOR? OR CELL? OR STEM?) AND (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR)
S9	389	RD (unique items)
S10	25	S9 AND PY=1994
S11	57	S9 AND PY=1995
S12	57	RD S11 (unique items)
S13	0	(ENDOTHELIAL) (5N) (PROGENITOR? OR STEM?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR) (20N) (TOGETHER OR COMPOSITION)
S14	1	(ENDOTHELIAL) (5N) (PROGENITOR? OR STEM?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR)
S15	206	(ENDOTHELIAL) (5N) (CELL?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR)
S16	3	(ENDOTHELIAL) (5N) (CELL?) (20N) (NUCLEIC) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR) (20N) (COMPOSITION? OR FORMULATION? OR TOGETHER OR COMBIN?)
S17	2	RD S16 (unique items)
S18	1696	(ENDOTHELIAL) (5N) (CELL? OR PROGENITOR? OR STEM?) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR) (20N) (COMPOSITION? OR FORMULATION? OR TOGETHER OR COMBIN?)
S19	898	(ENDOTHELIAL) (5N) (CELL? OR PROGENITOR? OR STEM?) (10N) (MITOGEN OR VDGF OR FGF OR FACTOR) (10N) (COMPOSITION? OR FORMULATION? OR TOGETHER OR COMBIN?)
S20	50	S19 AND PY=1994
S21	26	RD S20 (unique items)
S22	52	S19 AND PY=1995
S23	23	RD S22 (unique items)
S24	100	(ENDOTHELIAL) (5N) (CELL? OR PROGENITOR? OR STEM?) (20N) (MITOGEN OR VDGF OR FGF OR FACTOR) (10N) (DNA OR NUCLEIC) (20N) (COMPOSITION? OR FORMULATION? OR TOGETHER OR COMBIN?)
S25	54	RD S24 (unique items)
S26	0	S25 AND PROGENITOR?
S27	1	S25 AND STEM
S28	771	ENDOTHELIAL(5N) (PROGENITOR? OR STEM?)
S29	65	S28 AND REVIEW?
S30	41	RD S29 (unique items)
S31	0	S30 AND (THERAP?OR TREAT?)
S32	13	S30 AND (THERAP? OR TREAT?)
S33	13	RD S32 (unique items)